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Effect of oxidative stress on cognitive functions in children with obesity

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ABSTRACT

Objectives: This study aims to evaluate the relationship between the oxidative stress induced by obesity and metabolic changes in the cognitive functions of obese children.

Methods: Thirty-three obese children and adolescents (age: 8-18); and 33 healthy children similar in terms of age and gender were enrolled. Children were diagnosed with obesity according to the Turkish children's body mass index (BMI) curves. Patients over the 95th percentile in terms of Turkish children's BMI curves considering their genders and age were called obese children. Obese children were excluded whose obesity was related to any syndrome or disease. Neurocognitive functions including the Visual Memory Test, Finger Tapping Test, Memory Test, Symbol Digit Coding, Stroop Test, Continuous Performance Test, and Shifting Attention Test were evaluated with the battery tests of Central Nervous System Vital Signs (CNSVS) via computer. Malondialdehyde (MDA) and protein carbonyl (PC) were analyzed to determine the oxidative stress. After 10 hours overnight fast, blood samples were collected to determine Fasting glucose, total cholesterol, triglyceride, low-density lipoprotein, high-density lipoprotein, liver enzymes aspartate aminotransferase and alanine aminotransferase by using enzymatic methods.

Results: MDA and PC levels in obese children were founs significantly higher (0.78±0.16 µmol/L;198.30±84.45 nmol/mL) than the controls (0.5±0.10 µmol/L; 125.35±43.52 nmol/mL) (P<0.001). All of the cognitive performance domains were statistically significantly different between the study and control groups. A statistically significant correlation was found between neurocognitive indexes and MDA and PC levels.

Conclusions: Obese children's cognitive functions must be evaluated. Elevated oxidative stress may be the reason for the bad cognitive performance in children with obesity. However, this cognitive performance study in obese children should be supported with large study groups.

Keywords: Oxidative stress, cognition, obesity, children

Childhood obesity is a remarkable clinical situation among children with devastating health consequences. It is linked with adult obesity and other complications such as diabetes mellitus, hypertension, hypercholesterolemia, and metabolic syndrome [1, 2]. Now it is understood that obesity is more than a weight management problem. Reduced cognitive functioning has also been reported to be a promi-

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nent complication in children and adolescents with obesity in recent years [3, 4].

Oxidative stress emerges from the imbalance between the prooxidant state and the antioxidant defense system. Free radicals are continuously produced during daily metabolism [5]. They are highly reactive and may diminish cell function by damaging lipids, proteins, and other macromolecules of the cell [6]. Lipids are the most targeted molecules by oxidative stress through all other classes of biomolecules. Malondialdehyde (MDA) is the end product of lipid peroxidation and a major marker of oxidative stress. It interacts with certain proteins in the cell and also nucleic acid bases to form different adducts [7].

Fat tissue is an important source of reactive oxygen products. During the process of excess free fatty acids in mitochondria uncoupling may occur and electron transfer to oxygen may not be completed [8]. Fat accumulation has been shown to be associated with oxidative stress, and a study by Furukawa *et al* found that levels of antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPx) were reduced in obese individuals [9]. Substances modified by oxidation have also been found to accumulate in adults with obesity [10]. Studies related to oxidative stress in childhood obesity suggest similar findings. In this context, Codoner-Franch *et al*. [11] have proposed a risk of metabolic syndrome in children with obesity because of fat tissue-induced oxidative stress.

The brain is highly susceptible to oxidative damage, and lipid peroxidation is abundant in white and gray matter. Increased oxidative stress in the brain tissue is likely to play a role in cognitive impairment. Some antioxidants have been also shown to attenuate cognitive impairment in experimental studies [12, 13]. As evidenced above, there is a relationship between obesity and oxidative stress but the effect of oxidative stress on cognitive functions in obese children is less clearly lightened. The study goal is to understand oxidative stress' effects on the cognitive status of children and adolescents with obesity in this study.

METHODS

Participants

We included two groups of obese children and healthy controls in this study. Obese children were evaluated in the pediatric department of a university hospital inner northern of Türkiye. Thirty-three children with obesity were selected age between 8 to 17 years. Children with any health problems or syndrome were not included in the obese children group. A healthy control children group was conducted with similar ages and genders from healthy children policlinic of pediatrics department. The control group was conducted from thirty-three children with normal BMI. Informed consent was obtained from all participants and/or their parents. This research study was approved by Gaziosmanpasa University (Tokat, Türkiye) Medical Research Ethics Committee (Date: 30.03.2016 and number: 16-KAEK-043/2016-04)

Measurements

Anthropometric Measurements

Measurements were made using a measurement system (Seca Corp, Chino, CA, USA) while the patients were barefoot and wearing light clothes. Height was measured using an internal stadiometer (Seca). Body Mass Index (BMI) was calculated by dividing weight in kg by the square of height in square meters (kg/m²). Obesity was identified according to Turkish children's BMI percentiles and if the percentile was >95th percentile considered obesity [14].

Laboratory measurements

Fasting glucose (FG), total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL), high-density lipoprotein (HDL), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were determined by using an autoanalyzer (COBAS 6000; Roche Diagnostics, Indianapolis, IN, USA). C-reactive protein (CRP) and ferritin were detected by electrochemiluminescence immunoassay (COBAS C-501&E-601; Roche Diagnostics).

Determination of MDA and PC levels

The position of serum thiobarbituric acid reactive substance (TBARS) was determined by a system predicated on a response with thiobarbituric acid (TBA) at 90-100°C that was previously described by Esterbauer and Cheeseman [15]. In the TBA test response, MDA or MDA- suchlike substances and TBA reply to produce a pink color with an absorption outdoors at 532 nm. The response was performed at pH 2-3 and 90°C

for 15 min. The sample was mixed with a double volume of cold 10 (w/v) trichloroacetic acid to precipitate the protein. The precipitate was rolled by centrifugation (1,500 × g for 10 min) and an aliquot of the supernatant was replied with an equal volume of 0.67 (w/v) TBA in a scorching water bath for 10 min. Following cooling, the absorbance at 532 nm was measured (GBC Cintra 10e UV/ VIS Spectrophotometer, Victoria, Australia). Results are expressed in ng/ml, according to the graphic standard prepared from measures with a standard result (tetramethoxypropane). The carbonyl contents were determined spectrophotometrically (Shimadzu UV-160 A, Tokyo, Japan) by a system predicated on response of carbonyl group with 2, 4-dinitrophenylhydrazine to form 2, 4-dinitrophenylhydrazone. 2, 4- dinitrophenylhydrazine was the reagent originally used for proteins vanquished to substance-catalyzed oxidation [16].

Central Nervous System Vital Signs (CNSVS)

A neurocognitive test method using with computer The CNSVS is used in this clinical research. The manner of the neuropsychological tests and the psychometric characteristics of this test battery are very similar and the validity and reliability have been demonstrated [17]. This CNSVS test can be used after 7 years of life. Cohen's d sample ranged from d = 0.44 to d = 1.19 for repeat-retest reliability in children and adolescents [18]. This test only can be used with a computer and the total time to complete the test is approximately 30 to 40 minutes. Seven common neuropsychological measures were evaluated in this test: Visual Memory Test, Symbol Digit Coding (SDC), Verbal Memory Test, Finger Tapping Test (FTT), Stroop Test (ST), Continuous Performance Test (CPT), and Shifting Attention Test (SAT). To calculate seven domain scores (Memory, Psychomotor speed, Processing speed, Reaction time, Complex attention, Executive Function, and Cognitive flexibility) and a summary score (Neurocognition Index-NCI) test creates 15 primary scores.

Procedure

Children were diagnosed with obesity according to the Turkish children's BMI curves. Patients over the 95th percentile in terms of Turkish BMI curves considering their genders and age were called obese children. Obese and healthy children completed 2 visits. In the first visit, participants completed the CNSVS test via computer in a silent room near with one of the parents. One week later blood samples were collected from participants in the second visit.

Statistical Analysis

Test scores were compared by the SPSS package program (IBM SPSS Statistics 18). Values are presented as n (%) or mean±SD. Independent samples t-tests were used for continuous variables compared between two groups. Pearson correlation coefficient was used to correlate variables. P values less than 0.05 were considered significant.

RESULTS

The obese children group consisted of 33 patients (18 females, 15 males) with a mean age of 11.58±2.22 years. The control group was conducted with 33 children. The gender and age of healthy participants are similar to the obese group. There is no difference between the two groups considering number, gender, and age (P>0.05).

Table 1 shows the demographic, anthropometric characteristics, and biochemical test results for the group differences. BMI-(standard deviation score) SDS was higher in children and adolescents with obesity (P<0.05). LDL of obese children group was significantly higher and HDL was significantly lower than the healthy control group (P<0.05). Mean CRP was 6.86±5.35 mg/dL and 3.45±2.32 mg/dL in the obese study and healthy control groups, respectively (P<0.05).

The mean MDA and PC levels for the obesity group were 0.78±0.16 µmol/L and 198.30±84.45 nmol/mL, respectively, while the mean MDA and PC levels for the control group were 0.5±0.10 µmol/L and 125.35±43.52, respectively (P<0.001). There was a statistically significant difference in terms of the mean MDA and PC levels between the obesity and control groups (P<0.001). The characteristic scores of the different groups are shown in Table 2.

Eight index scores of the CNSVS were evaluated in two groups and groups were compared. It was found that there was a statistically significant difference between obese children and healthy groups on all cog-

Table 1. Demographic, anthropometric characteristics and laboratory measurements

	Obesity (n=33)	Control (n=33)
Genders (Male/Female)	15/18	15/18
Age (years)	11.58±2.22	11.89±2.79
BMI-SDS	2.43±0.29	1.21±0.44*
Fasting glucose (mg/dL)	87.48±10.73	87.22±10.27
ALT (U/L)	21.91±9.09	22.5±12.95
AST (U/L)	24.39±5.24	23.08±8.39
Total cholesterol (mg/dL)	161.48±29.43	159.49±36.11
LDL-cholesterol (mg/dL)	103.83±29.07	87.30±29.42*
HDL-cholesterol (mg/dL)	45.49±10.72	52.46±14.26*
Trygliceride (mg/dL)	113.42±46.16	111.72±41.64
CRP (mg/dL)	6.86±5.35	3.45±2.32*
Ferritin (ng/mL)	41.33±19.51	39.3±11.2

Data are shown as mean±standard deviation or frequency (n). BMI=body mass index, SDS=standard deviation score, ALT=alanine aminotransferase, AST=aspartat aminotransferase, LDL=low density lipoprotein, HDL=high density lipoprotein-cholesterol, CRP=C-reactive protein

nitive domains. The mean NCI score belonging to obese children was 83.27±9.74 compared to 96.64±4.59 for healthy children. It is seen that obese children's NCI scores were statically lower than healthy children (P<0.001). Also, the other components of cognitive functions measured with this test

Table 2. Distributions of characteristics according to patient and control groups

	Obesity (n=33)	Control (n=33)	Bonferroni 95% CI	
			Lower	Upper
MDA (µmol/L)	0.78±0.16	0.5±0.10*	-	-
PC (nmol/mL)	198.30±84.45	125.35±43.52*	-	-
Neurocognition index	83.27±9.74	96.64±4.59*	7.91	18.82
Composite memory	87.7±10.69	98.88±8.45*	4.28	18.08
Verbal memory	89.58±12.45	101.33±11.10*	3.32	20.20
Visual memory	88.36±10.61	97.91±7.17*	3.06	16.03
Processing speed	86.61±10.43	98.82±5.75*	6.19	18.24
Executive function	82.88±14.67	99.36±6.75*	8.31	24.66
Psychomotor speed	86.67±10.10	96.88±6.83*	4.04	16.38
Reaction time	75.12±13.96	97.15±8.54*	13.75	30.32
Complex attention	84.58±17.49	100.52±6.09*	6.57	25.31
Cognitive flexibility	82.03±16.69	98.21±7.43*	6.94	25.43

Data are shown as mean±standard deviation. MDA=malondialdehyde, PC=protein carbonyl
Hotelling's T2 test was used for Bonferroni 95% confidence intervals. *P<0.05

Table 3. Correlations of oxidative and metabolic parameters with cognition indexes

		PC (n=66)	MDA (n=66)	CRP (n=66)	LDL (n=66)	HDL (n=66)
Neurocognition index	r	-0.118	-0.475	-0.115	-0.279	0.291
	P value	0.355	**<0.001**	0.374	**0.023**	**0.020**
Composite memory	r	-0.257	-0.348	-0.106	0.027	0.161
	P value	**0.042**	**0.004**	0.414	0.829	0.205
Verbal memory	r	-0.288	-0.396	-0.056	0.023	0.080
	P value	**0.022**	**0.001**	0.665	0.856	0.532
Visual memory	r	-0.133	-0.291	-0.136	0.006	0.278
	P value	0.299	**0.018**	0.291	0.962	**0.026**
Processing speed	r	-0.071	-0.436	-0.248	-0.159	0.177
	P value	0.580	**<0.001**	0.052	0.202	0.163
Executive function	r	-0.112	-0.391	0.039	-0.320	0.228
	P value	0.382	**0.001**	0.763	**0.009**	0.070
Psychomotor speed	r	-0.104	-0.389	-0.208	-0.094	0.032
	P value	0.418	**0.001**	0.104	0.453	0.804
Reaction time	r	-0.250	-0.460	-0.230	-0.366	0.325
	P value	**0.048**	**<0.001**	0.073	**0.003**	**0.009**
Complex attention	r	-0.092	-0.403	-0.057	-0.247	0.225
	P value	0.472	**0.001**	0.661	**0.046**	0.074
Cognitive flexibility	r	-0.106	-0.347	0.055	-0.294	0.237
	P value	0.408	**0.004**	0.670	**0.017**	0.060

MDA=malondialdehyde, PC=protein carbonyl, CRP=C Reactive protein, LDL=low density lipoprotein-cholesterol, HDL=high density lipoprotein-cholesterol

were statically lower in children with obesity than in healthy controls (P<0.001).

MDA levels were correlated inversely with all cognitive indexes (P<0.05). Composite memory, verbal memory, and reaction time were correlated negatively with PC values (P<0.05). No significance was detected between CRP levels and any of the cognitive domains although it was inversely correlated with almost all cognitive indexes. LDL negatively and HDL positively were correlated with NCI score (P<0.05). Besides, LDL was negatively correlated with, complex attention, executive function, reaction time, and cognitive flexibility (P<0.05). It is found that there is a positive correlation between HDL and visual memory, and reaction time (P<0.05). Correlation values are shown in Table 3.

DISCUSSION

In the literature, the numbers of studies on cognitive functions in obese children show that bad cognitive performance is linked to obesity. Many of the studies using different assessment methods demonstrate a big association between obesity and bad cognitive performance.

Regarding the role of obesity on cognitive functions in young women, Bove *et al*. [19] found a significant negative association between the visceral adipose tissue and the cognitive domains of verbal learning and memory. Low cognitive scores of 37,414 young Danish men were found to be associated with obesity [20]. There are several studies investigating the relationship between obesity and cognitive impair-

ment in the elderly, however, the results are conflicting [21-24]. On the other hand, cognitive functioning in childhood obesity has been examined in a limited number of studies. These studies prove that a tight conjuctionn between obesity and cognitive disfunction. Mean reaction time was associated with BMI and about 30% of the genetic variance between reaction time performance and BMI were shared in a study comprising 1,312 twins aged 7-10 [25]. Preadolescent children with high BMI were found to have poorer academic scores. Adiposity and school performance were inversely related [26]. Impairment in visual-spatial organization and general mental abilities in children has also been associated with an increase in body weight [27]. Studies demonstrated a poor relationship between neurocognition and obesity in the preschool period [28]. This study examined the effects of oxidative stress on cognitive functions in obese children. The results show that obese children and adolescents performed worse than healthy controls on all cognitive measures. We found a correlation between the reduced neurocognitive functions and the increased oxidative stress in the obesity group.

Given this poor functioning in individuals with obesity, studies investigated the associated factors between obesity and reduced cognition. However, the effect of oxidative stress on reduced cognitive functions in obese children and adolescents is less clearly established. We found a significant increase in lipid oxidation and protein oxidation in the obesity group in this context. High MDA and PC levels were correlated with reduced cognitive domains; MDA for all domains and PC for the memory and reaction time domains.

Increased adipose tissue in obesity is a rich source of cytokines, hormones, and other similar molecules released by the fat tissue. Such diseases like diabetes mellitus and metabolic syndrome are likely to develop by a process triggered by these molecules in children with obesity. The central nervous system (CNS) is more sensitive to changes in childhood since this period is critical for brain development. Therefore, CNS-related problems caused by obesity should be illuminated.

Regarding lipid peroxidation, children and adolescents with obesity had higher levels of MDA compared to the healthy controls in this study. MDA is one of the most studied lipid electrophiles generated from lipid peroxidation [29]. Brain disorders have been usually evaluated in terms of lipid peroxidation because the axonal membranes and myelin sheaths of the brain are rich sources of lipids. Moreover, The central nervous system is susceptible to oxidative stress due to high oxygen consumption. Lower antioxidant status has been associated with impaired cognition in the institutionalized elderly [22]. In addition, circulating adipose tissue cytokines are associated with oxidant-antioxidant status. Carbonyl proteins have been used to present oxidative damage to proteins. This enhances thermodynamic instability inducing tertiary structural changes. Thus, protein aggregation or inactivation emerges. It was reported that restoring PC formation with antioxidant agents could improve cognitive function [30]. PC levels were significantly associated with cognitive impairment in a postmortem study examining the frontal cortex of individuals [30]. In agreement with these findings, we found that PC levels of obese children and adolescents were higher than the healthy controls and there was a negative correlation between PC levels and cognitive functions, particularly memory and reaction time.

We evaluated several biochemical parameters and found that CRP, LDL, and HDL cholesterol levels were significantly different in the obesity group. LDL levels were statically higher while the HDL levels were statically lower in the obesity group. LDL is the principal lipoprotein particle for the transport of cholesterol to the peripheral tissues. LDL plays an important role in the atherosclerotic process and the pathogenesis of Alzheimer's disease [31, 32]. It is suggested that elevated levels of LDL lead to memory deficits. HDL possesses important functions such as anti-oxidation, anti-inflammation, pro-endothelial function, anti-thrombosis, and modulation of immune function. Low HDL was associated with poorer cognitive performance in very old adults. Another study found better executive function in 60-year-old individuals with higher HDL levels [33-35]. Supporting these data from the elderly, we found a negative correlation for LDL and a positive correlation for HDL regarding the cognitive parameters of children and adolescents with obesity. Executive function, reaction time, complex attention, and cognitive flexibility were found to be negatively correlated with LDL while visual memory and reaction time were positively correlated with HDL. To our knowledge, this is the first study suggesting the association between LDL-HDL cholesterol

levels and cognition in pediatric obesity.

Chronic low-grade inflammation has been reported in obesity. Inflammation has also been shown to impact cognition in several psychiatric disorders like anxiety disorders, major depressive disorder, and bipolar disorder [36]. However, no study has been conducted on the inflammation-related cognitive decline in obesity. So we also investigated the association between CRP levels and cognitive functioning in the obesity group. We found elevated CRP levels in the obesity group but we did not find a correlation between the CRP levels and the cognitive domains.

Limitations

Our study has several limitations that should be addressed. We could only evaluate the CRP levels of the children and adolescents to indicate inflammation. Other inflammatory markers or proinflammatory cytokines may be analyzed in future studies. A larger study group would be better for estimating regression analysis. Despite these limitations, we reported cognitive decline along with elevated oxidative stress and an inverse relationship between MDA and all cognitive domains in obese children in this study.

CONCLUSION

Oxidative stress should be evaluated when assessing the complex mechanism of this decline in the neurocognitive functioning of obese children and adolescents. Data regarding the effect of lipid peroxidation and protein oxidation on cognitive functioning may lead to new future intervention strategies for cognitive impairment in youth with obesity.

Authors' Contribution

Study Conception: SÖ; Study Design: SÖ, İB; Supervision: SÖ, HB; Funding: N/A; Materials: SÖ, İB, HB; Data Collection and/or Processing: SÖ, İB, HB; Statistical Analysis and/or Data Interpretation: SÖ, HB; Literature Review: SÖ, İB, HB; Manuscript Preparation: SÖ and Critical Review: SÖ, İB, HB.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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